REMARKS

Claim Amendments

Applicants would like to thank the United States Patent and Trademark Office for the favorable Decision on Petition, dated August 3, 2004, withdrawing the telephonic Restriction Requirement, dated September 13, 2000, and the finality of the final Office Action, dated April 10, 2003. As a result of the withdrawals, the present Office Action, dated August 20, 2004, is an examination of the merits of all claims from the two restricted groups (i.e., Claims 1-26). However, Applicants note that Claim 14 had been canceled in the Amendment B, mailed to the U.S.P.T.O. on January 14, 2002.

Claims 1 and 16 have been amended to include the amendments previously made to Claims 11 and 24. Support for the amendments can be found, for example, at page 11, lines 5-6.

Claims 1, 11, 16 and 24 have been amended to recite that the RNA set forth in each Claim is total RNA and that the DNA probes set forth in each Claim are cDNA probes. Support for total RNA can be found, for example, on page 33, line 3 of the specification. Support for cDNA probes can be found, for example, on page 11, lines 5-14 of the specification.

Claims 1, 11, 16 and 24 also have been amended to recite a method of identifying a gene or genes involved in transcription-dependent memory comprising performing a statistical comparison using ***a*** signal detected in a control, in order to provide proper antecedent basis. Support for the amendment can be found, for example, on page 3, lines 10-11 of the specification.

Rejection of Claims 1-10 and 16-23 Under 35 U.S.C. § 112, First Paragraph

Claims 1-10 and 16-23 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to disclose the manner and process of making and using the claimed invention, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. In particular, the Examiner asserts that "the specification, while being enabling for identifying genes involved in transcription-dependent memory in drosophila, does not reasonably provide enablement for non-human animals." In the Examiner's assessment, it would require undue experimentation to

practice the claimed invention with a reasonable expectation of success because of (1) the quantity of experimentation necessary; (2) the lack of working examples; (3) the unpredictability of the art; (4) the lack of sufficient guidance in the specification; and (5) the breadth of the claims.

Applicants respectfully disagree with the Examiner's assessment that the claimed invention is not enabled. The standard for enablement under 35 U.S.C. § 112, first paragraph, is whether the claimed invention can be practiced without undue experimentation given the guidance presented in the specification and what was known to the skilled artisan at the time the subject application was filed. A specification is not required to teach what is well known in the relevant art at the time the subject application was filed. See, e.g., Lindemann Maschinenfabrik G.m.b.H. v. American Hoist & Derrick Co., 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); In re Wands, 8 U.S.P.Q.2d 1400, 1402 (Fed. Cir. 1988).

In addition, a specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. In re Borkowski, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). See also M.P.E.P. § 2164.02. The Federal Circuit has held that "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." Gould v. Quigg, 3 U.S.P.Q.2d 1302, 1304 (Fed. Cir. 1987) (quoting In re Chilowsky, 108 U.S.P.Q. 321, 325 (C.C.P.A. 1956)). A specification which contains a teaching of how to make and use the full scope of the claimed invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

Existence of Working Examples; State of the Prior Art; Breadth of the Claims

In the Office Action, the Examiner asserts that "the specification does not provide working examples of the broadly claimed genus of non-human animals that would enable one of ordinary skill in the art to make and use the invention as claimed" (Office Action, page 5), and "the prior art and the specification do not teach or describe training protocols and/or conditions

sufficient to induce transcription-dependent memory in non-human animals as instantly claimed" (Office Action, page 4).

Applicants respectfully disagree. In the specification as filed, Applicants teach that memory exists in two basic forms, a transcription-independent form, which includes short-term memory, and a transcription-dependent form, which is associated with long-term memory (see specification, e.g., page 8, line 26 to page 9, line 5). Each form of memory can be elicited using known training protocols performed under controlled experimental conditions. Applicants' invention is based on the discovery that genes involved in long-term memory formation can be identified by subjecting a non-human animal to a particular training protocol, monitoring gene expression in the animal, and comparing the gene expression in the animal to the gene expression in a suitable control animal, using molecular techniques that are clearly described in the specification (see specification, e.g., page 10, line 2 to page 11, line 22).

For example, general behavioral training procedures for inducing long term memory formation are described in the specification on page 8, lines 16-25. Associative learning (commonly known as Pavlovian conditioning) can be used to establish a specific memory, by presenting two different stimuli in close temporal succession. One stimulus is an unconditioned stimulus (US), which triggers a reflex or innate physiological response when presented to an organism. The other stimulus is referred to as a conditioned stimulus (CS), which does not trigger an innate response. During a training session, the CS and US are presented, as a pair, in temporal contiguity. Associative learning takes place when the animal begins to "associate" the CS with the US, thereby responding to the CS either in the absence of or prior to presentation of the US.

In the specification as filed, Applicants disclose that specific forms of memory, e.g., transcription-dependent and transcription-independent forms, can be induced by administering training during either spaced or massed sessions (see specification, e.g., page 10 lines, 2-21; page 19, lines 21-28; page 20, lines 1-8; and page 22, lines 11-17). Massed training sessions, which do not elicit transcription-dependent memory, are administered in close succession with no rest interval, also referred to as an intertrial interval (ITI), between sessions. In contrast, spaced training sessions are administered with a rest interval between each session and are required for transcription-dependent memory formation. In the specification as filed, Applicants also teach

that the "differential effects on long-lasting memory produced by spaced versus massed training is a phenomenon widely observed in the animal kingdom" (see specification, e.g., page 19, lines 21-22).

A specific training protocol for Drosophila is depicted in Figure 1 of the application and is described in Tully *et al.*, Cell 79: 35-47 (1994) and Tully and Quinn, *J. Comp. Physiol.*, 157:263-277 (1985), both of which are incorporated by reference into the specification (see specification, page 11, lines 2-5). Specifically, a classical Pavlovian odor-shock procedure is performed in which flies are exposed to a CS (e.g., an odor) paired with a US (e.g, electrical shock). The paired stimuli are then followed by the presentation of a second odor that is not paired with an electric shock. The stimuli are presented to the flies during either spaced or massed training sessions, to establish experimental and control groups, respectively. Following the training sessions, the flies are placed into an apparatus, wherein both odors are presented, one on each end of the apparatus. Memory is assessed by monitoring which odor the flies migrate towards.

The specification also discloses methods for testing memory formation in rats, utilizing a training protocol that is fundamentally similar to the Drosophila protocol (see specification, e.g., Examples 9-11 and 16). Using this protocol, transcription-independent and transcription-dependent forms of memory are induced by presenting rats with paired CS-US stimuli (e.g., light pulse and electrical foot-shock), as part of a Pavlovian conditioning procedure. Similar to the Drosophila protocol, the stimuli are presented during either massed or spaced training sessions to induce transcription-independent or transcription-dependent memory. Memory is tested after completion of the training protocol by monitoring the response of the rats to the CS (light pulse) when presented in the absence of the US.

In addition, at the time of Applicants' invention, it was known that:

> Studies of ***many species*** have shown that when training involves multiple trials, the time interval between trials is an important variable in the efficacy of accumulating training effects and the strength of retention (Carew et al. 1972; Fanselow and Tighe 1988; Tully et al. 1994; Spiegler and Balota 1996; Kogan et al. 1997; Hermitte et al. 1999; Muzzio et al. 1999; Beck et al. 2000; Wu et al. 2001). The paradigms tested were taste aversion conditioning, fear conditioning, blink conditioning, olfactory aversion training, episodic priming, and learning nonsense syllables. ***In addition to humans, a wide range of animals was studied***

(*Drosophila*, the marine mollusks *Aplysia* and *Hermissenda*, the crab *Chasmagnathus*, rats, and rabbits). (Menzel, R. *et al., Learning and Memory, 8*: 198-208 (2001), being provided herewith as the Exhibit; see page 198, columns 1 and 2, emphasis added).

These examples illustrate that training protocols sufficient to induce transcription-dependent memory in a wide variety of non-human animals were known to those skilled in the art at the time of Applicants' invention. Therefore, the scope of the claimed invention is consistent with the specification, which teaches training protocols applicable to the broad genus of non-human animals.

Nature of the Invention; Level of Predictability in the Art; Quantity of Experimentation Required

In the Office Action, the Examiner relies on Applicants' teaching that "specific training protocols are expected to yield CMGs in animals" (see specification, e.g., page 20, line 9) to support the enablement rejection. Specifically, the Examiner states that the differences between the training of Drosophila and rats "illustrates the nature of the invention is such that species-specific conditions are required to induce transcription-dependent memory" (Office Action, page 4) and that "the ability to predict specific protocols for training the very large and divers[e] genus of non-human animals would be very low" (Office Action, page 5). The Examiner concludes that "it would require undue experimentation for one skilled in the art to make and use the invention as claimed" (Office Action, page 6).

Applicants respectfully disagree. Applicants' teaching that "specific training protocols are expected to yield CMGs in animals" refers to the use of spaced versus massed training, which is "a phenomenon widely observed in the animal kingdom" (see specification, e.g., page 19, line 22). As indicated in Applicants' specification and in the prior art, such massed versus spaced training and/or conditions sufficient to induce transcription-dependent memory or transcription-independent memory in non-human animals, as instantly claimed, are well known to those of skill in the art. Although the training protocols described for Drosophila and rat models are not identical, both share basic and essential features that can be applied, in general, to training protocols for inducing transcription-independent and transcription-dependent forms of memory in any non-human animal. In particular, both protocols utilize Pavlovian conditioning (a CS and

a US are presented in temporal contiguity) to induce memory formation. Specifically, the CS is odor for the Drosophila protocol and a light pulse for the rat protocol, while the US in both protocols is electrical shock. Although specific CS-US pairs are used in the protocols described in the specification, any of a variety of other paired CS-US stimuli should produce similar results. In one example, the odor-electrical shock CS-US pair described in the Drosophila protocol could be used in training protocols for rats and other mammals.

Furthermore, as discussed in the specification in both cases, transcription-dependent or transcription-independent memory formation is generated by administering training during spaced or massed sessions, respectively (see specification, e.g., page 10, lines 2-21; page 19, lines 21-28; page 20, lines 1-8; and page 22, lines 11-17). In the Office Action, the Examiner asserts that the specification teaches "protocols for rats requiring specially designed cages and startle chambers" (Office Action, page 4). However, such specialized cages and chambers are used for the purpose of presenting stimuli and assessing a response, not for inducing transcription-dependent memory, which is achieved by the use of spaced training sessions. These specialized apparati are not required for inducing transcription-dependent memory, and represent only a subset of many, known possible devices that could be used for such training procedures.

Therefore, the specification teaches that a general training protocol comprises presenting paired conditioned and unconditioned stimuli (to induce memory formation in general), during either spaced or massed training sessions (to induce specific forms of memory, e.g., transcription-dependent or transcription-independent). In addition, as pointed out above, the prior art clearly indicates that such general training protocols were well known to those of skill in the art at the time of Applicants' invention. One of skill in the art is clearly able to devise a suitable training protocol, using an appropriate CS-US pair, for any given non-human animal. Intertrial time periods for spaced and massed training sessions are also well known to those of skill in the art and can be determined empirically (e.g., by testing a range of time periods, as described in Examples 10 and 16 of the specification).

It would not require undue experimentation for one skilled in the art to devise and administer training protocols for the purpose of eliciting transcription-dependent memory formation in non-human animals in order to identify a gene or genes involved in transcription-dependent memory, as described in the subject specification.

Applicants have provided an enabling disclosure for the full scope of the claimed invention.

Rejection of Claims 1-26 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-26 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out, and distinctly claim, the subject matter which Applicants regard as the invention. Certain claims have been amended in response to the rejection. The amendments are not intended to narrow the scope of the claims. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, second paragraph.

As amended, the indicated claims include the following changes, made in response to the specific rejections made by the Examiner:

Claims 1-10 are rejected as being "indefinite in Claim 1, (b) and (c) for the recitation RNA, but it is unclear whether total RNA is extracted. DNA is synthesized from the RNA in step (c) which suggests...the DNA is cDNA." Claim 1 has been amended in steps (b) and (f)(ii) to clarify that the RNA is "total" RNA, and in steps (c), (d), (f)(iii) and (f)(iv) to indicate the "DNA" probes are "cDNA" probes. Claims 1-10 are also rejected as being "indefinite in Claim 1, step (f) for the recitation 'the signal detected in a control' because the recitation lacks proper antecedent basis in the claim." Claim 1, step (f) has been amended, as helpfully suggested by the Examiner, to replace "the signal detected in a control" with "a signal detected in a control."

Claims 11-15 are rejected as being "indefinite in Claim 11, (b) and (c) for the recitation RNA, but it is unclear whether total RNA is extracted." Claim 11 has been amended in steps (b) and (f)(ii) to clarify that the RNA is "total" RNA. Claims 11-15 are also rejected as being "indefinite in Claim 11, step (d), for the recitation 'DNA probes' because the recitation lacks proper antecedent basis in the 'cDNA probes' of step (c)." Claim 11 has been amended in steps (d) and (f)(iv) to replace "DNA" probes with "cDNA" probes. Furthermore, Claims 11-15 are rejected as being "indefinite in Claim 11, step (f) for the recitation 'the signal detected in a control' because the recitation lacks proper antecedent basis in the claim." Claim 11, step (f) has been amended, as helpfully suggested by the Examiner, to replace "the signal detected in a control" with "a signal detected in a control."

Claims 16-23 are rejected as being "indefinite in Claim 16, (b) and (c) for the recitation RNA, but it is unclear whether total RNA is extracted. DNA is synthesized from the RNA in step (c) which suggests...the DNA is cDNA." Claim 16 has been amended in steps (b) and (f)(i) to clarify that the RNA is "total" RNA, and in steps (c), (d), (f)(ii) and (f)(iii) to indicate the "DNA" probes are "cDNA" probes. Claims 16-23 are also rejected as being "indefinite in Claim 16, step (f) for the recitation 'the signal detected in a control' because the recitation lacks proper antecedent basis in the claim." Claim 16, step (f) has been amended, as helpfully suggested by the Examiner, to replace "the signal detected in a control" with "a signal detected in a control".

Claims 24-26 are rejected as being "indefinite in Claim 24, (b) and (c) for the recitation RNA, but it is unclear whether total RNA is extracted." Claim 24 has been amended in steps (b) and (f)(i) to clarify that the RNA is "total" RNA. Claims 24-26 are also rejected as being "indefinite in Claim 24, step (d), for the recitation 'DNA probes' because the recitation lacks proper antecedent basis in the 'cDNA probes' of step (c)." Claim 24 has been amended in steps (d) and (f)(iii) to replace "DNA" probes with "cDNA" probes. Furthermore, Claims 24-26 are rejected as being "indefinite in Claim 24, step (f) for the recitation 'the signal detected in a control' because the recitation lacks proper antecedent basis in the claim." Claim 24, step (f) has been amended, as helpfully suggested by the Examiner, to replace "the signal detected in a control" with "a signal detected in a control."

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No.: 40,564
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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